Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients

An assessment of need

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1 Methodology

The National Institute for Health Clinical Excellence (NICE) received a remit from the Department of Health "To produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients". The National Collaborating Centre for Cancer (NCC-C) developed the scope for the guidance after a process of consultation with stakeholders. The scope for the guidance was approved by NICE and published in September 2010. A Guidance Development Group (GDG) was subsequently established to develop the guideline in line with NICE methodology (NICE, 2009, NICE 2012).

The guideline covers children and adults with cancer (including haematological malignancies) that are receiving anti-cancer treatment and are therefore at risk of neutropenic sepsis and covers services in all settings where NHS care is received. The scope covers bacterial causes of sepsis only (www.nice.org.uk).

As part of this process a needs assessment was commissioned. The purpose of this report is to inform the development of guideline recommendations by providing a description of the current burden of neutropenic sepsis and service provision in England and Wales.

This needs assessment has focussed on health care facilities delivering anti-cancer chemotherapy and where a patient presenting with neutropenic sepsis may be assessed or treated (adult cancer units, adult cancer centres, adult haematology-oncology units levels 1-4, paediatric primary treatment centres and paediatric oncology shared care units levels 1-3).

Neutropenia or neutropenic sepsis not caused by anti-cancer treatment is excluded from the scope.

The terms "neutropenic sepsis" and "febrile neutropenia" are often used interchangeably, although lack of a standard definition means each term may be interpreted differently. In this document, "neutropenic sepsis" will be used throughout to mean the development of fever, often with other signs of infection, in a patient with neutropenia. All literature and internet searches in this needs assessment used both terms - "neutropenic sepsis" and "febrile neutropenia".

2 Introduction

The purpose of this guideline is to ensure prompt and effective management of cancer patients presenting with neutropenic sepsis, as well as advising on prevention and diagnosis of this important complication of anti-cancer treatments. It is a significant cause of mortality and morbidity and causes delays and dose reductions to planned treatment. The greatest risk of neutropenic sepsis is with cytotoxic chemotherapy. The Guideline Development Group (GDG) recognises the importance of distinguishing uncomplicated neutropenic fever from neutropenia with severe sepsis and shock, and indeed septic shock can occur without fever. In clinical practice the terms febrile neutropenia and neutropenic sepsis are used interchangeably in this patient group and recommendations within this document use the term "neutropenic sepsis" to indicate the full range of severity of illness.

The neutrophil or granulocyte forms part of the innate immune system. Normally they constitute 60-70% of the total leukocyte count. They circulate in the blood and are found inactive in the bone marrow. Neutrophils respond early to signals reporting injury or infection, migrating to the affected area. They have a role in both directly killing non-host cells such as bacteria by phagocytosis and chemical damage via degranulation, and activating other parts of the immune system, for example T cells (Nathan, 2006, Witko-Sarsat *et al*., 2000). They have a circulating life span of between 8 hours and 5 days (Pillay *et al*., 2010), and take approximately six days to enter circulation from the bone marrow (Dancey *et al*., 1976).

Cytotoxic anti-cancer chemotherapy is designed to kill neoplastic stem cells by damaging the DNA irreparably. The mechanism behind this damage varies according to the chemotherapy drug. The more rapidly dividing normal tissues such as hair follicles, mucosal linings and bone marrow cells can also be affected, causing the well documented toxicities of alopecia, mucositis and bone marrow suppression leading to neutropenia, anaemia and thrombocytopenia. For the majority of chemotherapy regimens, the neutrophil count falls to its lowest level approximately 5-7 days after administration of chemotherapy (Holmes, 2002) and can take up to 2-4 weeks to recover, although for some drugs and regimens, these timescales are considerably different. There is a tendency for neutropenic sepsis to occur more commonly in the first two cycles of treatment Lyman, Delgado, 2003). While novel biological agents generally have a lower rate of neutropenia than cytotoxic chemotherapy, such problems can still occur.

When neutropenic, the patient is vulnerable to invasive infection (Bhatt, Saleem, 2004) which can potentially cause overwhelming sepsis and death. Deterioration can be very rapid, sometimes without an obvious focus for infection. Reported mortality for untreated neutropenic sepsis ranges from 2 to 21% (Herbst *et al*., 2009). Neutropenic sepsis is therefore considered a medical emergency, and as with severe sepsis and septic shock from any cause, there is widespread agreement that early administration of broad spectrum antibiotics and management of shock is key to successful management (Rivers, *et al*., 2001). There is almost no universal agreement about the details of many aspects of the care of a patient with neutropenic sepsis, although there are many common themes Phillips *et al*., 2007).

There are various strategies for preventing neutropenic sepsis. Primary prophylaxis aims to prevent first episodes of neutropenic sepsis, and secondary prophylaxis is a strategy used to prevent subsequent episodes. Granulocyte colony stimulating factors (GCSF), antibiotics, and alterations to the cytotoxic regimen are the main prophylactic strategies.

Recently neutropenic sepsis has been highlighted as an area of clinical priority in the UK, initially by a publication from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD, 2008) then by a subsequent report from the National Chemotherapy Advisory Group (NCAG 2009).

In 2008, NCEPOD published "For better or for worse? A review of the care of patients who died within 30 days of receiving anti-cancer therapy" (NCEPOD, 2008). This report looked at the deaths of patients within 30 days of chemotherapy, and highlighted aspects of care which could be improved. Recommendations covered the development of appropriate clinical care pathways and local policies, staff training and timely availability of antibiotics. A specific recommendation was made for antibiotics to be given within 30 minutes of presentation to patients with suspected neutropenic sepsis and shock.

Following the NCEPOD report, NCAG published "Chemotherapy Services in England: Ensuring quality and safety" (NCAG 2009). The aim of the report was "to bring about a step change in the quality and safety of chemotherapy services in England, taking account of the concerns from peer review and from NCEPOD". Key recommendations made included the introduction of acute oncology provision, appropriate patient education and access to emergency advice and healthcare. A "door to needle" time of one hour was recommended for antibiotics to be administered in cases of suspected neutropenic sepsis.

Current practice concerning the management of neutropenic sepsis has also been influenced by many other international recommendations, guidelines and studies.

The Surviving Sepsis Campaign (Dellinger *et al*., 2008) has produced international guidelines for the management of severe sepsis, including severe neutropenic sepsis. It recommends early investigations such as blood cultures and serum lactate, early administration of antibiotics (within 30 minutes), and goal directed resuscitation.

A number of risk scores, which have influenced some current guidelines have come into use over the past few years. These include scores to identify those patients at both high and low risk of severe sepsis.

The Modified Early Warning Score (MEWS) (Subbe *et al*., 2001) has been validated to identify seriously unwell adult patients within general medical wards rather than those specifically with neutropenic sepsis, but it and similar scoring systems are in widespread use.

There are several specific risk scores for neutropenic sepsis which have the aim of identifying those patients at especially low risk of developing severe sepsis, meaning that less aggressive treatment than has been "traditional" may be appropriate. These cover both adults Klastersky *et al*., 2000) and children (Alexander *et al*., 2002).

The details surrounding the treatment and prevention of neutropenic sepsis in published literature vary greatly. There is also no universally agreed definition of "neutropenia" and "sepsis" in this context amongst published literature (Clarke *et al*., 2011).

Table 2.1 illustrates this lack of agreement in publications and trials.

Table 2.1: Differing definitions of neutropenic sepsis in published literature

Paper	Definition of Neutropenia	Definition of sepsis	Reference
Cancer Therapy Evaluation Common Toxicity Criteria, Version 2.0	Grade 1: ≥1.5 - <2.0 x 10^9/l Grade 2: ≥1.0 - <1.5 x 10^9/l Grade 3: ≥0.5 - <1 x 10^9/l Grade 4: <0.5 x 10^9/l	n/a	Marrow *et al*., 1999
Link *et al*	<500/µl or <1000/µl with predicted decline to 500/µl	temperature of ≥ 38.3°C or ≥ 38.0°C for at least 1 h, or measured twice within 12 hours	Link *et al*., 2003
Martin *et al*	Grade 4 neutropenia	fever ≥ 38.1°C	Martin *et al*., 2006
Darryl *et al*	neutrophil count ≤ 1.0 X 10^9/l	oral temperature of ≥ 38.2 °C	Maher *et al*., 1994
Ammann *et al*	ANC < 0.5 × 10^9/l or ANC < 1.0 × 10^9/l and expected to decline	axillary temperature of ≥ 38.5°C persisting for at least 2 h, or a single measurement of ≥ 39.0°C	Ammann *et al*., 2004
Woll *et al*	WBC count , 1.0 x 10^9/l	temperature ≥ 37.5°C	Woll *et al*., 2001

3 The Epidemiology of Neutropenic Sepsis in England and Wales

3.1 Incidence of Neutropenic Sepsis

The incidence of neutropenic sepsis in England and Wales is difficult to determine with any degree of certainty, because of the variations in definition of neutropenic sepsis and lack of a consistent code used on NHS clinical coding databases.

As will be seen in subsequent sections, there is no agreement across the country regarding the definition of neutropenic sepsis, making the interpretation of any local audits or studies difficult to apply nationally.

Theoretically, the incidence of neutropenic sepsis could be captured from NHS clinical coding databases using ICD10 codes. Neutropenic sepsis however, is not coded for by a single code. The combination of four codes is required in order to identify neutropenic sepsis caused by anti-cancer chemotherapy. Agranulocytosis (D70), Malignancy (C00-C97), Sepsis (A40-41) or any other code implying infection (of which there are many), and anti-cancer drugs causing adverse affects in therapeutic use (Y43.1 to Y43.3) (www.who.org.uk) are all required to code for the condition.

Although a single study in Wales (North Wales Cancer Network Audit) showed a reasonable correlation between the findings of a prospective audit and clinical coding information in that region, it is the experience and consensus of the GDG that nationally, clinical coding information could not be relied on to produce a result which would be meaningful to individual institutions planning their services. One major North London hospital submitted an audit which used clinical coding to capture patients with neutropenic sepsis. It found that at least 13% were incorrectly coded for neutropenia, without it being possible to determine how many patients were not coded who should have been (unpublished data).

During the development of the guideline, the GDG suggested that a national audit should be carried out to assess the incidence of neutropenic sepsis in a given time period. In view of the time required to undertake a national audit of neutropenic sepsis incidence or even audit a representative number of institutions, it was decided that this was too large a project to undertake for this needs assessment.

Nationally, audits and service reviews have addressed the subject of neutropenic sepsis and assessed the impact of the condition on individual hospitals, cancer networks and regions. These have not been nationally coordinated, used different methodologies, different criteria for diagnosing neutropenic sepsis and covered differing clinical environments, from a single ward to an entire cancer network. In order to gain an insight into the burden of neutropenic sepsis, a selection of audits were reviewed. Audits were gathered from three main sources – peer reviewed publications, an internet search of locally published (non-peer reviewed) audits and from supporting documents returned with a national questionnaire survey (see chapter 4). Internet and literature searches were for the terms “audit” AND (“neutropenic sepsis” or “febrile neutropenia”). Only audits which recorded the total number of neutropenic sepsis admissions over a given period of time from centres in England or Wales were included.

Table 3.1: Summary of audits and reviews of rates of neutropenic sepsis

Time period	Number of cases	Audit description	Source
05/2007 – 08/2007	71 admissions in 64 patients	Audit of all patients admitted with neutropenic sepsis to the seven hospitals of the South West London Cancer Network (population 1.4 million)	Okera *et al*., 2011
2 months	29 patients	Single institution audit at John Radcliffe Hospital, Oxford of patients admitted either to A&E or haematology.	Richardson *et al*., 2009
1 year (2008)	128 episodes in 119 patients	Single institution service improvement audit for an adult haematology department (no solid tumours) of episodes of neutropenic sepsis on the haematology ward.	Van Vliet *et al*., 2011
1 year (1/4/04 to 31/3/05)	762 episodes in 368 patients	4 Paediatric Oncology Centres (averaging 74.7 episodes each) and 43 Paediatric Oncology Shared Care Units (averaging 13.5 episodes each) in London	Dommett *et al*., 2009
1/1/2009 to 31/3/2009	32 episodes	3 hospitals of the North Wales Cancer Network	Okera *et al*., 2011
6 months	22 patients admitted through A&E	Mainly haematology patients in an adult cancer unit / haemato-oncology unit.	Submitted from survey
January 2008 to April 2009	42 episodes	Audit of a North-London general hospital with a cancer unit and adult haemato-oncology unit using coding for neutropenia to select cases.	Submitted from survey
08/2010 to 10/2010	33 patients	Haematology and oncology unit in East London – two other audits from this hospital displayed similar results.	Submitted from survey
03/2011 to 06/2011 inclusive	92 cases in 84 patients	Admissions to a Yorkshire Cancer centre for cancers treated there or in nearby cancer units (including some lymphoma but no other haemato-oncology)	Submitted from survey

These surveys demonstrated busier specialist units admit over 20 patients a month with neutropenic sepsis, while the burden on general hospitals is considerably less – approximately three patients per month. These rates will vary hugely depending on population size, tumour types treated locally, chemotherapy regimens used and local demographics.

Consideration should be given to performing a national prospective audit to capture all incidences of neutropenic sepsis and identify the burden of disease in the UK.

3.2 Mortality from Neutropenic Sepsis

The most important adverse outcome from an episode of neutropenic sepsis is the death of the patient. As part of this report, a study has been undertaken to assess the reported death rates from neutropenic sepsis over the past 10 years.

Methods

On the death of a patient, information from the Medical Certificate of Cause of Death is coded and recorded by the Office of National Statistics (ONS). A search of the ONS database was undertaken to identify patients coded as having died with an underlying cancer diagnosis between 2001 and 2010 where both an infection and neutropenia were also reported on the death certificate. This means that “Neutropenic Sepsis”, “Febrile Neutropenia” and “Neutropenia and Pneumonia”, for example, would all have been captured. The search was performed using ICD10 codes rather than plain text. The numbers of patients recorded as having died from neutropenic sepsis was also compared to the number of cancer diagnoses in the same year in England (Office of National Statistics) and Wales (Welsh health statistics).

A selection of the records were checked visually by the ONS to ensure the ICD10 codes could be relied on in this situation, and false positives did not seem to occur. Unfortunately a full “free text” search of the ONS database was not possible, so we were unable to determine whether there were false negatives (patients incorrectly coded as not having had neutropenic

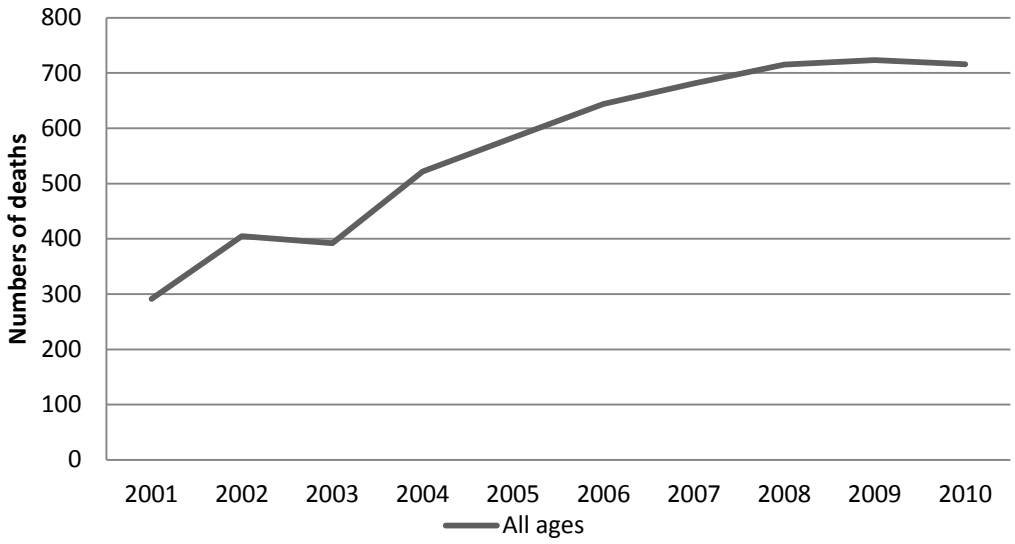
sepsis). Death rates were assessed between the years 2001 and 2010 inclusive. A summary of the ICD10 codes used in the search is listed in Appendix 1.

Results

Total Deaths from Neutropenic Sepsis

When combining the results for males and females of all ages over the past 10 years, the number of deaths where neutropenic sepsis was recorded on the death certificate has more than doubled. In 2001 there were 291 deaths with the cause of death recorded as neutropenic sepsis. In 2010 these had increased to 716. There is a significant positive relationship between the year and total number of NS deaths ($p<0.001$). Fitting fractional polynomials with the MFP package reported the best fit was achieved from a simple linear form. Figure 3.1 represents how recorded deaths from neutropenic sepsis have increased over time.

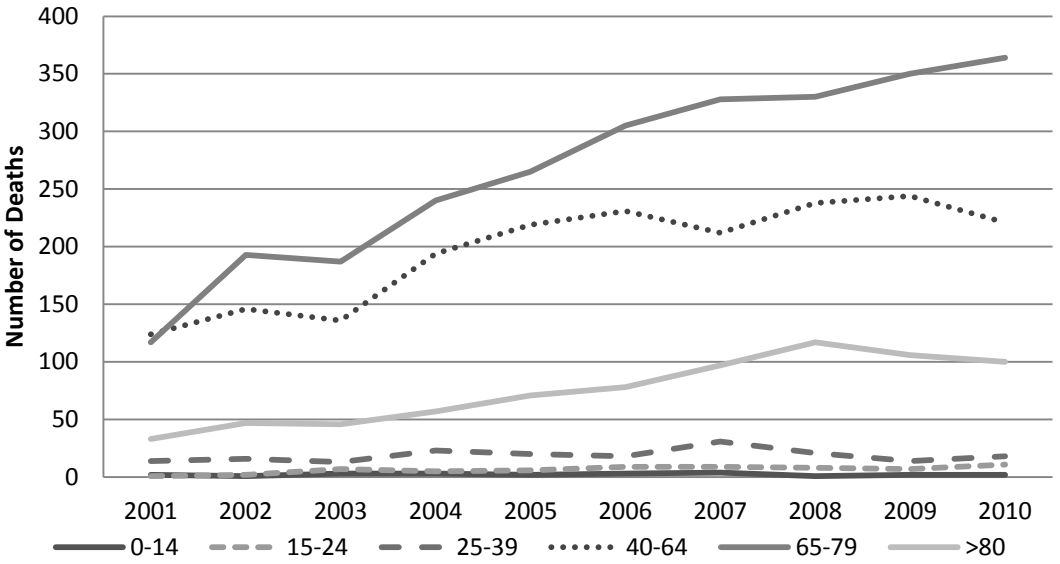
Figure 3.1: Total deaths from neutropenic sepsis, paediatric and adult, England and Wales 2001-2010.
Data source: ONS



Neutropenic Sepsis Deaths by Age

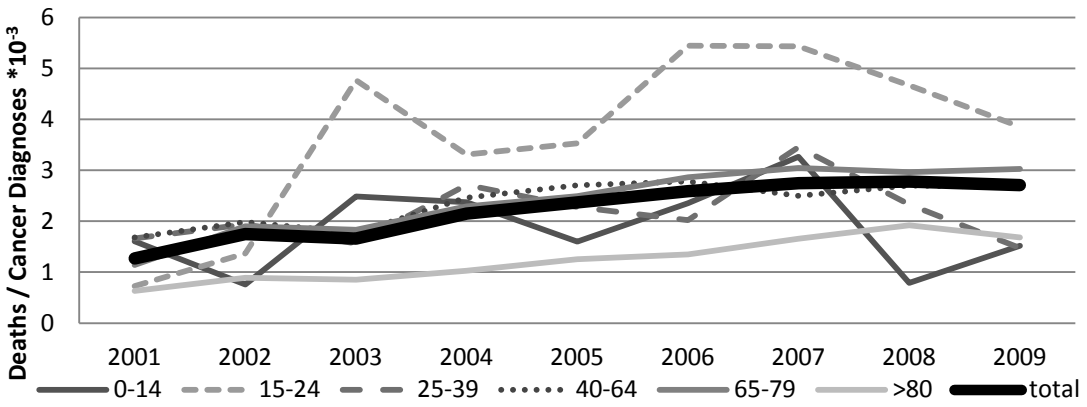
Figure 3.2 demonstrates the number of neutropenic sepsis deaths per age group. The age range 65 to 79 contains the majority of deaths. The rate of this increase has been assessed and has not found to differ across the age ranges examined.

Figure 3.2: Deaths from neutropenic sepsis by age group England and Wales 2001-2010.
Data source: ONS



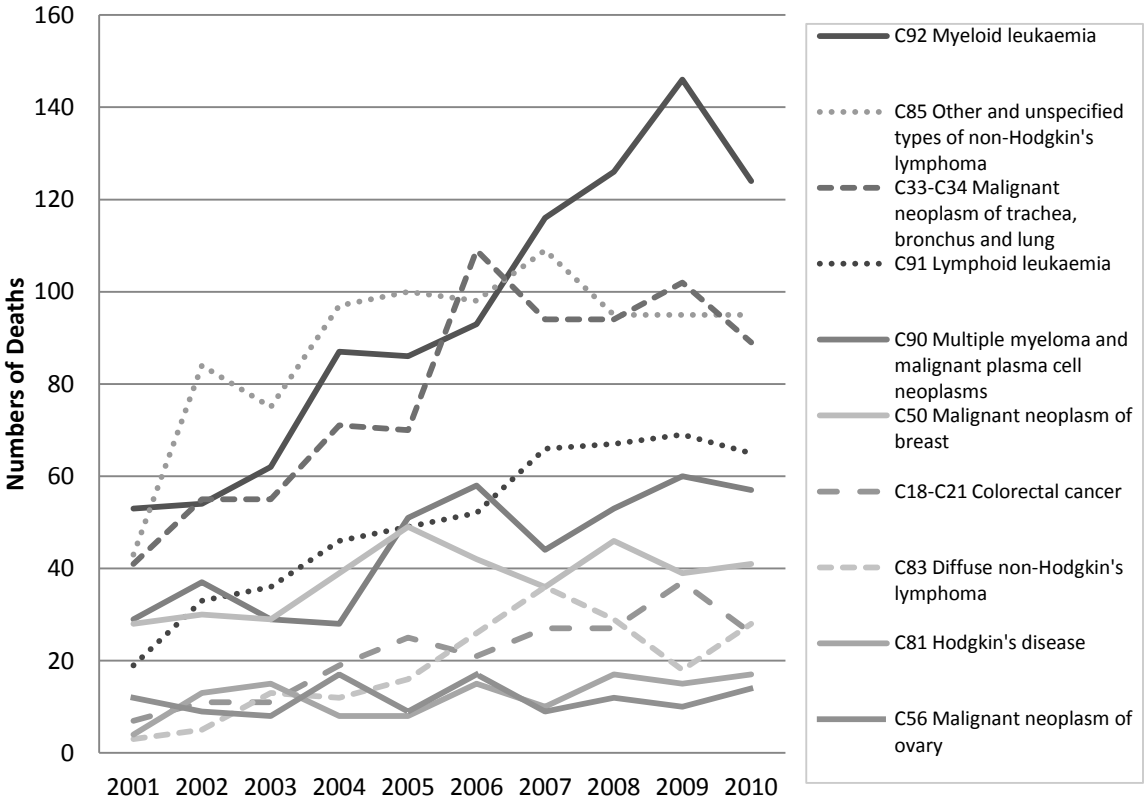
The number of deaths from neutropenic sepsis each year from 2000 to 2009 as a proportion of the annual total of cancer diagnoses (not including non-melanoma skin cancer) in each age group has been examined (Figure 3.3). Over this period, the total number of cancer diagnoses increased by 17%. Relative to the increased numbers of cancer diagnoses, the proportion of deaths due to neutropenic sepsis continues to rise for all groups. The rate of increase of neutropenic sepsis deaths is higher for the 15-24 year old age group, and lower for the >80 age group ($p < 0.05$, see Appendix 2 for detail). It should be noted that the total number of deaths in the 15-24 age group is very low - 58 deaths from neutropenic sepsis in total between 2000 and 2009.

Figure 3.3: Ratio of numbers of neutropenic sepsis deaths to total cancer diagnoses by age group, England and Wales
Data source: ONS



When broken down into individual cancer diagnoses, the numbers of reported deaths from neutropenic sepsis can be seen to have increased between 2001 and 2010 for all cancers. The 10 most common cancers where death involved neutropenic sepsis are shown in Figure 3.4.

Figure 3.4: Absolute numbers of cancer deaths from neutropenic sepsis by diagnosis, (paediatric and adult) England and Wales 2001-2010.
Data source: ONS



Conclusions

The numbers of neutropenic sepsis deaths recorded by the ONS has more than doubled in 10 years, and there are now approximately two deaths each day in England and Wales from this complication of anti-cancer therapy.

There are several possible explanations for the increase in death rates. The numbers of cancers diagnosed each year is increasing, but as a proportion of those, the relative rate of neutropenic sepsis deaths also continues to rise. The NCAG report (NCAG 2009) stated that 60% more chemotherapy was given in 2006 than 2002. If this rise has continued, this alone is likely to be responsible for the increase in neutropenic sepsis deaths. Increasing intensity of chemotherapy regimens may be having an effect. It is also possible that more patients who previously might have been thought to have been too high risk for treatment are being given chemotherapy, and the NCEPOD report (NCEPOD, 2008) highlighted that selecting less fit patients for chemotherapy risks a higher rate of fatal complications, including neutropenic sepsis.

Patients aged 15 to 24 have a significantly higher risk of dying of neutropenic sepsis. It has been documented for many conditions that teenagers and young adults are less compliant with medical treatment and advice than older adults. This has certainly been seen for epilepsy (Asadi-Pooya, 2005) and diabetes (Cramer 2004) amongst others, and is likely to impact on chemotherapy compliance too (Gesundheit, *et al*., 2007). This, combined with the higher intensity of many of the chemotherapy regimens given for cancers of patients in this age group is likely to explain this finding.

Patients with a cancer diagnosis aged 80 or more have a significantly lower risk of dying of neutropenic sepsis. While there are still a large number of cancers diagnosed in this group, considerably fewer patients are fit enough to receive chemotherapy, thus reducing the overall risk of neutropenic sepsis.

The most common underlying cancer diagnoses for patients dying of neutropenic sepsis are haematological malignancies, which have a relatively high rate of neutropenic sepsis, and the common solid tumours affecting adults for which chemotherapy is commonly given.

It is well documented that the accuracy of death certificate completion has been poor (Swift, *et al*., 2002), and there have been recent drives to improve the quality and accuracy. Potentially, the increase in reported deaths may be due, at least in part, to increased accuracy of death certificate completion. There are currently pilot programs introducing a medical examiner role which may further improve the quality of the documentation. The intention is to introduce this system nationally by 2013.

It is unknown whether patients had a death certificate completed implying neutropenic sepsis which was not coded as such on the ONS database. Potentially, the increased death rate from neutropenic sepsis may in part be demonstrating an improvement in ONS coding accuracy, but there is no evidence either to support or refute this. Unfortunately, it was not possible to investigate this in more detail.

3.3 Influence of Chemotherapy Regimen on Neutropenic Sepsis

The risk of a patient developing neutropenic sepsis varies greatly according to the treatment regimen and, with certain regimens, whether prophylaxis has been given (Martin, 2006). Risk factors for neutropenic sepsis can include advanced age, poor performance status, poor nutritional status, underlying haematological malignancy and intensity of chemotherapy (Lyman, *et al*., 2005).

In 2006, as part of an American Society of Clinical Oncology (ASCO) guideline document, a review was performed of the published likelihood (from various clinical trials) of the occurrence of neutropenic sepsis with various cytotoxic chemotherapy regimens thought to be of intermediate or high risk. In 2010 the European Organisation for the Research and Treatment of Cancer (EORTC) published a similar document (Aapro, 2010) and also repeated the review. A selection of the more commonly used regimens to treat adult cancers in the UK is included in Table 3.2.

Table 3.2: Risk of neutropenic sepsis from differing chemotherapy regimens

Tumour site	Regimen	Likelihood of neutropenic sepsis (%)	Trial
Breast	TAC[1]	28.8	Martin, *et al*., 2005
	FEC100-T[2]	25	Head, *et al*., 2008
	FAC[3]	4.4	Martin, *et al*., 2005
Lung	Carboplatin / Etoposide	10-20	Crawford, *et al*., 2011
	Gemcitabine / Cisplatin	7	Cardenal, 1999
Colorectal	FOLFIRI[4]	11	Douillard, *et al*., 2000
	FOLFOX4[5]	6	Rotheberg, *et al*., 2003
Gastric / Oesophageal	EOX[6]	10	Cunningham, *et al*., 2010
NHL	CHOP[7]	35	Lyman, *et al*., 2003
Hodgkin disease	ABVD[8]	2-12	Vakkalanka, Link, 2011, **Schwenkglenks,** Pettengell, 2010
Germ cell	BEP[9] (including CBOP-BEP)[10]	18	Teoh, *et al*., 2006
Head and neck	TPF[11]	9	Vermorken, 2007

[1] Docetaxel 75mg/m^2, doxorubicin 50mg/m^2, cyclophosphamide 500mg/m^2 d1 of 21 day cycle
[2] Fluorouracil 500mg/m^2, epirubucin 100mg/m^2, cyclophosphamide 500mg/m^2, d1 of 21 day cycle for 3 cycles then docetaxel 100mg/m^2 d1 of 21 day cycle for 3 cycles
[3] Fluorouracil 500mg/m^2, doxorubicin 50mg/m^2, cyclophosphamide 500mg/m^2 d1 of 21 day cycle
[4] Either irinotecan 80mg/m^2, fluorouracil infusion (24h) 2300mg/m^2, calcium folinate 500mg/m^2 d1 weekly OR irinotecan 180mg/m^2, fluorouracil 400mg/m^2 bolus and 600mg/m^2 22 hour infusion and calcium folinate 500mg/m^2 d1 of 14 day cycle
[5] Oxaliplatin 85mg/m^2 d1, leucovarin 200mg/m^2, fluorouracil 400mg/m^2 bolus and 600mg/m^2 22 hour infusion d1 and 2 of 14
[6] Epirubicin 50mg/m^2, oxaliplatin 130mg/m^2 and d1 capecitabine 625mg/m^2 bd daily 21 day cycle
[7] Cyclophosphamide 750mg/m^2, doxorubicin 50mg/m^2, vincristine 1.4mg/m^2 d1 and prednisolone 100mg d1-5 of 21 day cycle
[8] Doxorubicin 25mg/m^2, bleomycin 10,000u, vinblastine 6mg/m^2 and dacarbazine 375mg/m^2 d1 and 15 of 28 day cycle
[9] Bleomycin, etoposide and cisplatin (exact doses not specified from this source)
[10] Bleomycin, etoposide, cisplatin, vincristine and carboplatin (exact dose and schedule not specified from this source)
[11] Docetaxel 75mg/m^2, Cisplatin 75 mg/m^2, fluorouracil 750mg/m^2, d1 of 21 day cycle

4 Current Service Provision for Neutropenic Sepsis in England and Wales

4.1 Methods

In order to determine the current practice concerning the prevention and treatment of neutropenic sepsis a questionnaire (Appendix 4) was distributed, via the cancer networks, to all acute trusts in England and Wales. It was requested that this questionnaire was completed by a senior clinician (doctor or nurse) from any institution which may have to assess or treat a patient at risk of neutropenic sepsis. Several supporting documents were also requested, including any neutropenic sepsis, GCSF or relevant antibiotic policy documents, patient information, audits involving neutropenic sepsis and teaching materials. Where an institution had more than one neutropenic sepsis policy (it was recognised that policies for paediatrics, solid adult tumours and adult haemato-oncology in the same institution could be different), it was requested that one questionnaire be completed for each policy, meaning some institutions were expected to return up to three questionnaires. The questionnaire covered all the main areas set out in the scope of the neutropenic sepsis guideline.

The questionnaire was initially piloted by the Guideline Development Group. Both the questionnaire and a covering letter are included in Appendices 3 and 4.

The questionnaire data was imported directly into a Microsoft Access database directly from the Microsoft Word form, and any questionnaires returned on paper were manually entered. Where a questionnaire entry appeared to be incorrect or included a typographical error, any submitted documentation such as local neutropenic sepsis protocols were analysed and if necessary a correction was made. A combination of Microsoft Access and Excel were then used to analyse the data. Statistical tests were performed in R (version 2.13.0). The range and scope of these questionnaire responses was described qualitatively or quantitatively as appropriate. Where included, percentages have been rounded to the nearest 1%.

4.2 Results

Demographics

A total of 80 valid questionnaires were returned. 73 (91%) of these were submitted as Word documents and the rest were transcribed manually. We received two questionnaires from one centre covering the same protocol, one of which was incomplete and was therefore removed from the analysis. 51 centres returned a single questionnaire, 11 returned two, 1 returned 3 and 1 returned 4 (as there was a separate policy covering lung cancer in this centre). The geographical distribution included representation from and all areas of England and Wales were represented. As the questionnaire was distributed via the cancer networks to the cancer leads for each hospital rather then directly to the trusts, it was not possible to determine a response rate.

There were two responses from institutions which did not have a neutropenic sepsis policy because they would never be in the position of admitting such patients. No questionnaire was returned, and these centres were excluded from further analysis.

These 80 questionnaires represented:

- 53 Adult solid tumour policies
  - 1 Stand-alone centre
  - 23 Cancer centres within an acute trust
  - 29 Cancer units

- 44 Haematology policies (Matthey, *et al*., 2009)
  - 15 Level 1
  - 19 Level 2
  - 10 Level 3&4 (including two level 4 units)

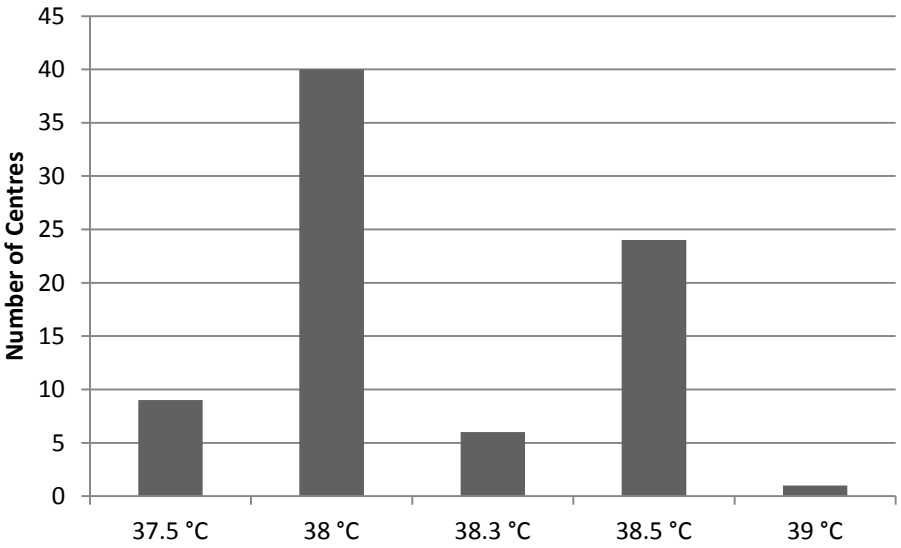
- 30 Paediatric oncology policies
  - 7 Primary treatment centres
  - 9 Level 1 shared care units
  - 4 Level 2 shared care units
  - 5 Level 3 shared care units
  - 5 Paediatric departments without oncology

Definition of neutropenic sepsis

Temperature criteria

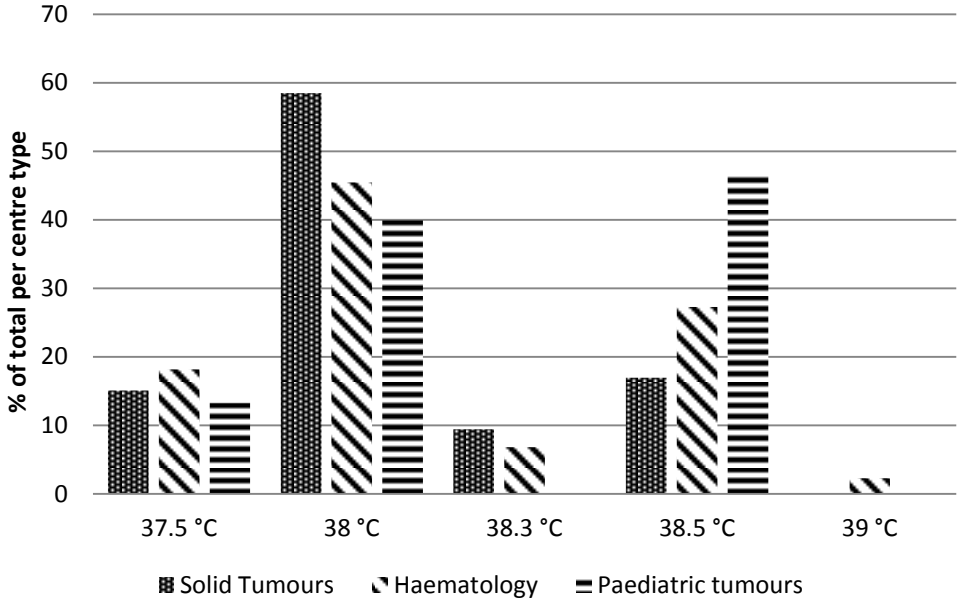
All centres had a single temperature above which the patient is considered to be at risk of neutropenic sepsis. The range of single readings varied from 37.5°C to 39°C. These are summarised in figure 4.1.

Figure 4.1: Single temperature defining neutropenic sepsis



When split into paediatrics, adult solid tumours and adult haematology, the most common single temperature used for adults is 38°C and for children is 38.5°C. A single haematology centre used 39°C. This is illustrated in Figure 4.2.

Figure 4.2: Single temperature defining neutropenic sepsis by centre type



In 36 (45%) protocols, two temperature readings recorded over a period of time of a slightly lower grade fever than the single reading described above would trigger a potential "neutropenic sepsis" diagnosis. Of these, 20 (56%) listed two reading of 38°C over one hour. There were nine different criteria listed in total ranging from two temperatures of 37.5°C in 2 hours (adult and paediatric) to two readings of 38° over 4 hours (all paediatric).

19 (24%) protocols also included a hypothermic temperature for defining potential neutropenic sepsis. Only 4 of these covered paediatric units.

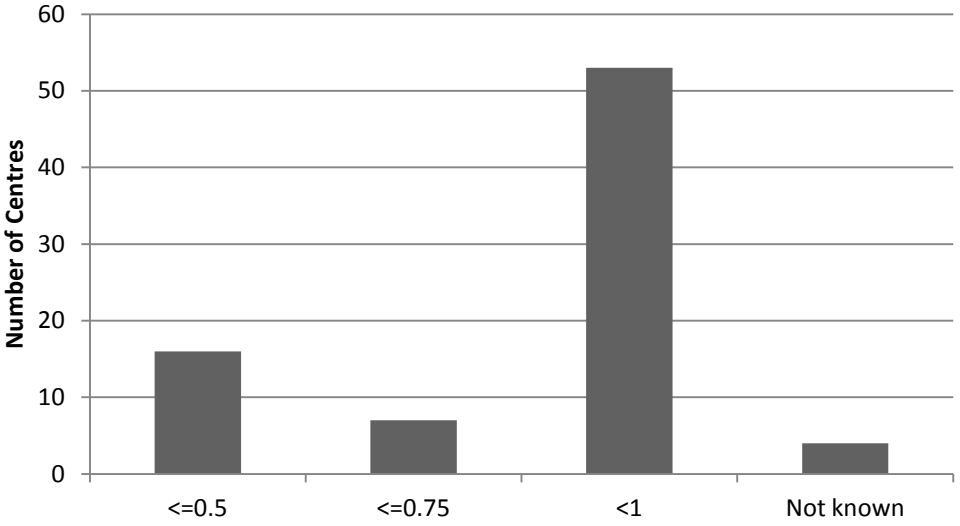
Table 4.1: Hypothermic temperatures used to define neutropenic sepsis

Minimum temperature	Number of protocols
36°C	14 (74%)
35°C	4 (21%)
34°C	1 (5%)

Neutropenia

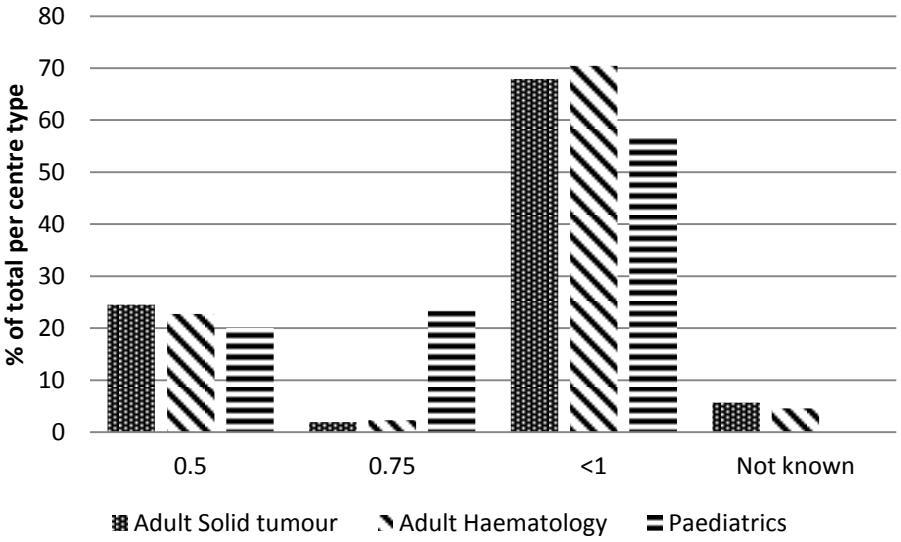
As with temperature criteria, the neutrophil count below which neutropenic sepsis was diagnosed varied between departments (See figure 4.3).

Figure 4.3: Neutrophil count diagnostic of neutropenia



When patient types were compared, there appeared to be little difference between paediatric, adult solid tumour and adult haematology criteria for neutropenia, except that a neutrophil count of 0.75x10^9/litre was more likely to be used in a paediatric centre. The proportions of centre types using each criteria is shown in Figure 4.4. A small number of centres also diagnosed neutropenic sepsis where there was a neutrophil count less than 1.0 x10^9/litre which was likely to decrease to 0.5 x10^9/litre, but this was never the only criteria.

Figure 4.4: Neutrophil Count diagnostic of neutropenia by patient group



Other criteria

The majority of protocols stated that if a patient was systemically unwell or shocked they would be treated as potentially having neutropenic sepsis regardless of the temperature. For the protocols where this was not explicitly stated, none suggested that a normal temperature excluded the diagnosis of neutropenic sepsis.

Prevention of neutropenic sepsis in adults and children

The two methods of prophylaxis against neutropenic sepsis covered by the guideline scope are antibiotics and GCSF. Chemotherapy dose or schedule alterations fell outside the scope of the guideline and were not asked for.

Prophylactic antibiotics – Primary Prophylaxis

This question concerned the indications for giving prophylactic antibiotics with the intention of preventing a first episode of neutropenic sepsis.

- 18 (23%) questionnaires stated their centres never give primary antibiotic prophylaxis
- 3 (4%) questionnaires stated primary antibiotic prophylaxis was given for all regimens (it was not possible to verify this with supplied documentation).
- Of the remaining 73%, there were widely varying indications for the use of primary antibiotic prophylaxis. These were generally "high risk" regimens. While there was little agreement about the precise details, some regimens and conditions were mentioned several times, for example:
    - Acute leukaemia
    - Various lung regimens
    - High risk breast cancer regimens (such as, TAC)
- Many gave antibiotic prophylaxis on cycle 1 alone

There was no clear difference in the pattern of usage of prophylactic antibiotics between paediatric, adult solid tumour and adult haematology centres.

The choice of prophylactic antibiotic was known for 35 policies. 77% used ciprofloxaxin and 23% used levofloxacin.

Prophylactic antibiotics – secondary prophylaxis

Following an episode of neutropenic sepsis, 31 (39%) respondents stated secondary prophylactic antibiotics would never be used, and 12 (15%) stated they would be used universally. The supporting documents for these were checked and no contradictions found, although in the majority of cases, secondary antibiotic prophylaxis was not specifically mentioned in the protocol. Where specified, ciprofloxacin was the commonest choice of antibiotic.

Prophylactic growth factors – primary prophylaxis

This question concerned the indications for giving prophylactic growth factors with the intention of preventing a first episode of neutropenic sepsis.

- 4 (5%) respondents stated their centres never used growth factors (adult solid tumour, adult haematology and paediatrics all represented).
- 3 (4%) respondents stated they used growth factors for all regimens (adult solid tumour and paediatrics represented), but it was not possible to verify this with supplied documentation.
- 39 (49%) protocols used growth factors for "high risk" regimens only.
- 8 (10%) protocols used them for only "high risk" potentially curative regimens.
- For the remaining 32%, criteria were very varied, and included
    - High risk of complications due to comorbidities or age
    - Higher risk regimens (as listed in antibiotic section)
    - Risk of neutropenic sepsis of >20%
    - Subjective criteria, for example "Consultant decision"

Where used for primary prophylaxis, GCSF (as opposed to GM-CSF) was always prescribed. Around 80% of protocols for primary GCSF prophylaxis used a once daily preparation and 20% used a long acting (pegylated) preparation for the majority of their regimens.

Prophylactic growth factors – secondary prophylaxis

Following an episode of neutropenic sepsis, 2 (3%) centres stated they never used growth factors, and 24 (30%) used them for all further cycles in the regimen to prevent further neutropenic sepsis. Policy varied considerably amongst the remainder of centres. Most of the GCSF used for this indication was given as a once daily preparation rather than pegylated.

Patient education

Written information

One centre did not administer chemotherapy and was excluded from this section of analysis. Of the remainder, 3 (4%) respondents stated their centres did not universally give written information including information about neutropenic sepsis prior to chemotherapy. At least one centre was developing such information when the questionnaire was completed, and others gave structured verbal information or written information after in-patient chemotherapy had been administered but prior to discharge. 57 (72%) gave written information at the initial visit, and the remainder gave the information at a subsequent clinic visit or just prior to chemotherapy. 51 (65%) routinely gave written information during more than one meeting.

It was requested that respondents to the survey return an example of chemotherapy patient information, to assess the information available to patients about neutropenic sepsis. 36 patient information leaflets were reviewed. Examples ranged from a 76 page patient-held record book covering all aspects of chemotherapy to single sided sheets reminding patients about neutropenic sepsis. The emphasis on neutropenic sepsis in the written information was varied. It was the sole topic for 10 (28%) leaflets. 20 (56%) highlighted it as an important topic, either because of emphasis placed on it in the text or its position in the printed information and 6 (16%) put no more emphasis on neutropenic sepsis than other chemotherapy toxicities. 29 (81%) information leaflets included advice concerning specific temperatures. 30 (83%) included a specific telephone number to call for advice. Other commonly raised topics included mouth care and diet. 4 examples of Macmillan Cancer Support leaflets (www.macmillan.org.uk) were also submitted. These were routinely used by many centres for information, especially for some rarer chemotherapy regimens. The Macmillan Cancer Support leaflets covering specific chemotherapy regimens include information about neutropenic sepsis in the body of the text with instructions to “contact your doctor or the hospital straight away” but no contact details are inherently part of these leaflets.

Verbal information before chemotherapy

All centres where chemotherapy was administered reported that verbal information concerning neutropenic sepsis was routinely given prior to chemotherapy, although 16 (20%) reported that chemotherapy could be delivered without it. 38 (48%) respondents reported their centres used a checklist while going through verbal information.

Chemotherapy alert cards

62 (78%) respondents reported their centre provided a card or letter designed to be carried at all times while on chemotherapy. Examples contained either information for the patient, management advice to healthcare professionals or both. 31 cards were reviewed. While the

majority were credit card sized, some were larger (still pocket sized) and there were a small number of examples of A4 sized letters.

- 67% were personalised to include the patient's name and 64% included the patient's unit number.
- 54% included the chemotherapy regimen, with 12% also including the dates of chemotherapy.
- 74% included a reminder to the patient of the symptoms of neutropenic sepsis or instructions on what to do if they felt unwell.
- 61% were designed to show to a health professional to give advice on treating neutropenic sepsis. This varied from including an abbreviated protocol including "door to needle" time to a reminder to check the hospital's neutropenic sepsis policy.
- 93% included a telephone number which could be called either by a health professional or the patient for advice.

Criteria for referral to secondary or tertiary care

This section focuses on the criteria which should trigger a referral (most commonly self-referral) to hospital for assessment of potential neutropenic sepsis. Four respondents did not provide an answer to this question. Of the remainder, 54 (71%) protocols specified the same temperature criteria as for diagnosing neutropenic sepsis in their centre and 21 (27%) used a lower temperature to trigger a referral. When there was a difference, the trigger temperature was usually between 0.3°C and 0.5°C lower than the diagnostic criteria, with one centre having a difference of 1°C. Two respondents reported a referral temperature higher than the diagnostic temperature, but it was not possible to verify whether this entry was made in error. 34 (44%) protocols included instructions that the patient seek help if they developed a low temperature.

No policy mandated that patients had to have a certain temperature before seeking assistance, and many protocols specified that help should be sought if the patient was feeling generally unwell, experiencing rigors or had other concerns.

Immediate management of neutropenic sepsis in adults and children

This section focuses on the immediate management plan for a patient presenting with suspected neutropenic sepsis.

Initial antibiotic timing

76 (95%) respondents reported antibiotics were routinely given to patients presenting with suspected neutropenic sepsis before the full blood count was known. Of these, 57 (75%) would recommend antibiotics were started in all patients, and the remainder would perform a risk assessment (using a risk stratification tool such as the MASCC criteria (Kern, 2006)) or clinical judgement.

75 (94%) respondents stated a "door to needle" time target was in place, and times were submitted for 73 (Table 4.2).

Several audits were submitted where door to needle time was evaluated. These tended to show that the "door to needle" time targets were initially poorly met, but improved on re-audit.

Table 4.2: Door to needle times

Door to needle time	Number of protocols
30 minutes	5 (7%)
1 hour	65 (89%)
2 hours	3 (4%)

Initial empirical intravenous antibiotic choice (where oral antibiotics are not being considered)

The questionnaire asked respondents about the empirical intravenous antibiotics used for suspected neutropenic sepsis in a number of situations.

When asked about the "standard" antibiotic choice when the patient was not classified as "high risk", did not have a central line in situ and was not allergic to penicillin, valid responses were submitted for 75 (95%) protocols. Of these, 27 (36%) use a single antibiotic while 48 (64%) used two or more antibiotics as their standard treatment. The regimens are listed in table 4.3.

Table 4.3 – Antibiotic protocols

Antibiotic regimen	**Number of protocols**
Piperacillin / tazobactam and gentamicin	43 (57%)
Piperacillin / tazobactam monotherapy	19 (25%)
Meropenem monotherapy	8 (11%)
Piperacillin / tazobactam and amikacin	3 (4%)
Ceftazadime and gentamicin	1 (1%)
Ceftriaxone and gentamicin	1 (1%)

The pattern of antibiotic use was generally the same in adult haematology, adult solid tumour and paediatric centres, although the two centres using ceftazadime or ceftriaxone with gentamicin were paediatric centres.

17 (21%) protocols used a risk assessment to identify those patients at higher risk of severe sepsis. 10 of these added gentamicin to the previous "standard" regimen and the 7 others changed to a completely different antibiotic regimen.

With a central venous catheter in situ where a line infection was NOT suspected, a different antibiotic regimen was recommended by 12 (15%) protocols. 9 added vancomycin and 3 added teicoplanin.

60 (75%) centres reported a specific policy for suspected central venous catheter infection. 33 added teicoplanin and 27 added vancomycin.

For a reported history of penicillin allergy but perceived low risk of anaphylaxis or angio-oedema, 64 (80%) protocols included a beta lactam-containing antibiotic such as ceftazadime or meropenem, while 12 (15%) policies contained no beta lactam antibiotics. For patients at high risk of penicillin related anaphylaxis, 28 (35%) respondents to the questionnaire quoted a regimen including a beta-lactam containing drug (mainly

meropenem). Where available, these policies were reviewed to confirm this aspect of the protocol.

Gentamicin was used in at least one situation in 62 (78%) protocols, and not used routinely in 18 (22%).

Some centres arrange for intravenous antibiotics to be administered either at home or in an outpatient setting on occasion (Teuffel, *et al*., 2011). No centres in this study reported delivering first line intravenous antibiotics for neutropenic sepsis in this way. Where intravenous antibiotics were administered out of hospital, it was for indications which could be treated with a once daily antibiotic (such as teicoplanin) for an organism which had been cultured and the sensitivities were known. Central line infections were the most commonly given indication.

Empirical oral antibiotics

In 23 (29%) protocols, empirical oral antibiotics were given to lower risk patients, with the intention of discharging them immediately, or at least earlier than would be the case for patients receiving intravenous antibiotics as an in-patient. This represented about a third of each of the paediatric, adult haematology and adult solid tumour protocols. Where a specific risk scoring system was given, the MASCC[1] score was most frequently quoted. Some high risk tumour types such as acute leukaemia were specifically excluded from receiving oral antibiotics in most of these regimens. Some centres only used such an oral antibiotic policy for palliative chemotherapy regimens. Where the patient had been on prophylactic oral antibiotics or GCSF they were generally excluded from receiving oral antibiotics to treat neutropenic sepsis. Ciprofloxacin and co-amoxiclav were the most common antibiotic choices, and 17 of the 23 protocols recommended both. Clindamycin was most commonly used if the patient was allergic to penicillin. Most centres using such a policy discharged patients immediately, with the minority observing for up to 24 hours (with one centre observing for 3 days). 10 of the 23 centres had specific written information for patients going home with empirical oral antibiotics.

On-going management of septic episode

Two situations were considered for the on-going management of neutropenic sepsis.

- "Uncomplicated" treatment of neutropenic sepsis, where the patient's pyrexia settles, neutrophil count increases and the patient can be discharged.
- Failure to respond to first line antibiotics.

Uncomplicated admission

Approximately two-thirds of centres of all types routinely switched from intravenous to oral antibiotics before discharge. Criteria for this switch varied greatly, including:

- Switching after a set number of days (from 1 to 5)
- Switching when the patient was apyrexial and had a rising neutrophil count
- Switching when the patient had been apyrexial for a given length of time, regardless of neutrophil count

The majority of centres observed the patient for 24 hours after stopping intravenous antibiotics before discharge. This was the case both if they had been changed to oral antibiotics or when antibiotics had been stopped completely.

[1] www.mascc.org

Failure to respond to first line empirical antibiotics

All centres reported that if the organism most likely to be causing the sepsis was cultured, antibiotics would be changed accordingly. The questionnaire asked how long a patient would remain on first line antibiotics without a clinical response before a change to second line empirical antibiotics would be considered. 54 (68%) protocols routinely changed the antibiotic regimen after 48 hours without improvement. 16 (20%) centres changed after 24 hours, and 10 (12%) considered changing after 3 or 4 days. The choice of second line empirical antibiotics fell outside the scope of the guideline remit.

Documentation concerning neutropenic sepsis

All but one centre had a written neutropenic sepsis policy, and all but two had a specific antibiotic policy for neutropenic sepsis.

Staff training

- 84% reported neutropenic sepsis was covered by the junior doctor induction, and 89% included it in ongoing junior doctor training
- 75% included neutropenic sepsis in a junior doctor handbook
- 84% included neutropenic sepsis in an ongoing nurse training program
- 97% of trusts included information about neutropenic sepsis on the internet, and 90% of respondents reported they thought it was easy to locate when needed
- 75% of trusts produced either posters or written information about neutropenic sepsis which was readily available to staff in the main admitting wards likely to receive neutropenic sepsis patients

5 Summary

Neutropenic sepsis is common, resulting in hundreds of hospital admissions every month and potentially causing the deaths of over 1 in 500 people diagnosed with cancer. There is evidence that the number of deaths from neutropenic sepsis is increasing at a faster rate than the number of cancers being diagnosed. The most likely explanation for this is the increase in the amount of chemotherapy administered in recent years (NCAG, 2009). If each chemotherapy cycle prescribed carries a risk of neutropenic sepsis, it is highly likely that the incidence, and therefore the rare event of a death from neutropenic sepsis will have increased too. Despite the very small numbers, there is a significantly greater risk of death from neutropenic sepsis in patients aged 15-24 years old.

Unfortunately it has not been possible to determine the overall burden of neutropenic sepsis on the NHS in England and Wales, largely because the GDG did not feel the accuracy of coding for neutropenic sepsis in clinical coding databases could be relied on at present, although it is recognised that efforts are being made to improve this.

Despite the significance of neutropenic sepsis and the national recognition of the importance of the condition, there is surprisingly little agreement throughout England and Wales regarding its definition, prevention, diagnosis and treatment. This echoes the findings of recent studies covering haemato-oncology (Clarke, *et al*., 2011) and paediatric oncology (Phillips, *et al*., 2007).

- Definitions of neutropenia ranged from a neutrophil count of $0.5x10^9$/litre to $1.0 x10^9$/litre. A temperature at which a patient would be treated empirically varied from 37.5°C to 39°C, with the majority using 38°C.
- Policies concerning prophylaxis with GCSF and/or antibiotics were very varied for both primary and secondary prophylaxis.
- Almost all centres had a “door to needle” time of one hour or less, when giving IV antibiotics to a patient suspected of having neutropenic sepsis, as mandated in the recent NCAG report (NCAG 2009). The antibiotics given varied considerably, but the majority of centres used either gentamicin and piperacillin / tazobactam or piperacillin / tazobactam alone.
- Approximately a third of centres had a policy where lower risk patients are given oral instead of intravenous antibiotics. Most patients were discharged immediately if started on this pathway.
- It was almost universal that patients received written and verbal information about neutropenic sepsis before chemotherapy was administered, or occasionally (in paediatric settings) before discharge following in-patient chemotherapy.
- Almost all centres had a written neutropenic sepsis policy, communicated to staff via training, posters, hospital intranets and handbooks.

A major methodological challenge in assessing the rate of neutropenic sepsis, infections and death in England and Wales was the variable quality and lack of consistency of death certification and clinical coding. This makes assessing the impact of neutropenic sepsis on patients, carers and the health service as a whole very difficult and probably impossible. While neutropenic sepsis is a complication of anti-cancer therapy rather than a diagnosis in itself, consideration should be given to assigning it a unique ICD10 code to better define the effect of this complication.

The dramatic variations seen here concerning the definitions, prevention and treatment of neutropenic sepsis seen here highlight the need for an evidence based guideline to guide and unify UK practice.

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Appendices

Appendix 1 – ICD 10 codes used by the Office of National Statistics to search for neutropenic sepsis related deaths;

Underlying cancer diagnosis (C00 to C97)

AND

Agranulocytosis (D70)

AND

Septicameia (A40-41) OR Pneumonia (J13, J14 J15 and J18)

The impact of using Y43.3 (toxicity caused by chemotherapy) was assessed, but produced very few results. It was felt that the above codes were sufficient to accurately identify the vast majority of deaths where neutropenic sepsis was listed as a contributory factor on the death certificate.

Appendix 2 – Statistical analysis of the cancer deaths from neutropenic sepsis compared with total cancer diagnoses.

The pairwise chi-squared test with Holm-Bonferroni correction was used to compare the total numbers neutropenic sepsis deaths to people diagnosed with cancer and not dying of neutropenic sepsis (deaths from other causes not considered) over a 9 year period. The data are illustrated graphically in Figure 3.3. Table A2.1 lists the p values for each age group compared to each of the others. Significant results (taken as $p<0.05$) are highlighted.

Table A2.1 - P values for ratio of neutropenic sepsis deaths to cancer diagnoses by age range

	0-14	15-24	25-39	40-64	65-79
15-24	0.0541				
25-39	1.0000	**0.0051**			
40-64	1.0000	**0.0117**	1.0000		
65-79	1.0000	**0.0140**	1.0000	1.0000	
>80	0.8409	**3.4×10^{-14}**	**8.9×10^{-09}**	**$< 2 \times 10^{-16}$**	**$< 2 \times 10^{-16}$**

The 15-24 age group has a significantly higher incidence of neutropenic sepsis deaths to cancer diagnoses than the others. Apart from the 0-14 age group, the >80 age group has a significantly lower incidence of neutropenic sepsis deaths.

Appendix 3 – Covering letter for Questionnaire

To: Trust Lead Cancer Clinician

Dear Colleague

Re: NICE clinical guideline on the 'Prevention and management of neutropenic sepsis in cancer patients'

The National Collaborating Centre for Cancer (NCC-C) has been commissioned by the National Institute for Clinical excellence (NICE) to develop a clinical guideline on the 'Prevention and management of neutropenic sepsis in cancer patients'. Further details of this project, including the guideline scope, can be found on the NICE website (http://guidance.nice.org.uk/CG/Wave23/11)

As part of the process for developing this guideline it is important for us to understand current practice in England and Wales regarding the prevention, assessment and treatment of neutropenic sepsis in patients undergoing systemic cancer treatment.

The method we are using to collect these data is via electronic questionnaire. Therefore we would be most grateful if you could arrange for the attached questionnaire to be forwarded to your chemotherapy lead physician or nurse for completion. The questionnaire also requests a number of documents (Appendix 1) which should be submitted at the same time as the questionnaire. If these documents do not exist for your organisation please could you let us know this as well.

If chemotherapy is not administered in your hospital, an emergency or acute medical physician may be in the best position to complete it. [We are aware that haematology, oncology and paediatric oncology departments in the same hospital might have differing protocols. If protocols are different, please arrange for the most appropriate person from each department to complete a questionnaire].

All information received will be analysed to provide important information on how these patients should be managed. Please be assured that the needs assessment is not an audit of the performance of individual institutions and all information returned will be kept and treated in strictest confidence and no hospital will be identifiable in the final guideline.

Finally we would ask that the completed questionnaire and requested documents are returned promptly via email no later than Monday 6th June 2011.

Many thanks

Professor Barry Hancock
Chair, Neutropenic Sepsis Guideline Development Group

Dr John Graham
Director, National Collaborating Centre for Cancer

Dr Timothy Simmons (Needs Assessment Lead)
SpR Oncology, Weston Park Hospital

Appendix 4 – Questionnaire

NICE clinical guideline on the 'Prevention and management of neutropenic sepsis in cancer patients'

QUESTIONNAIRE

Dear Colleague

Please find enclosed a copy of the questionnaire to support the development of the NICE clinical guideline on the prevention and management of neutropenic sepsis in cancer patients. We would be very grateful if you could complete this questionnaire electronically.

The questionnaire also requests a number of documents (Appendix 1) which should be submitted at the same time as the questionnaire. If these documents do not exist for your organisation please could you let us know this as well.

Please could you ensure that your completed questionnaire and other attached documents are returned promptly via email no later than Monday 6th June 2011. Please feel free to use this address if you have any other queries.

If you are unable to complete this questionnaire in one sitting, you can save it to your computer and return to it later

Many thanks in advance for your help with this project.

Yours faithfully

Dr Timothy Simmons (Needs Assessment lead)
SpR Oncology, Weston Park Hospital

Section 1 – General Information

Your name
Email address
Position

Trust name

Centre type	Adult Cancer Centre (stand alone)	☐
Please select the centre type	Adult Cancer Centre (Within Acute Trust)	☐
which *your* answers refer to.	Adult Cancer Unit	☐
	Adult Haematology oncology unit level 1	☐
If you have different protocols for	Adult Haematology oncology unit level 2	☐
Adult, haematological and paediatric	Adult Haematology oncology unit level 3	☐
oncology, please submit separate	Acute Hospital (no chemotherapy given)	☐
replies.	Paediatric Primary Treatment Centre	☐
	Paediatric Oncology Shared Care Unit level 1	☐
	Paediatric Oncology Shared Care Unit level 2	☐
	Paediatric Oncology Shared Care Unit level 3	☐
	Paediatric Department (no oncology)	☐

Other
Cancer Network

Section 2 – Patient Information and Criteria for Referral to Secondary / Tertiary Care

In order for a patient to be treated for sepsis, they first need to present for assessment. This section covers information given to the patient which might encourage them to present.

Is cytotoxic chemotherapy for cancer (as opposed to rheumatological, renal or other indications) administered in your institution? Yes
(If No, please move onto section 3)

Section 2a – Written Information

When being prepared for chemotherapy, do your patients receive **written** information about neutropenic sepsis? Yes

If Yes, when is this *generally* given (please tick all that apply)?

At initial visit when chemotherapy is first discussed	☐
At subsequent visit	☐
Just prior to chemotherapy administration	☐
Other	☐

If "Other"

Do some patients receive chemotherapy without written information? Yes

Please send an example of the written information used (see Appendix).

Do your patients carry "Alert Cards" regarding neutropenic sepsis? Yes

If so, please forward a copy.

Section 2b – Verbal Information

When being prepared for chemotherapy, do your patients receive **structured verbal** information about neutropenic sepsis? Yes

If Yes, when is this *generally* given?

At initial visit when chemotherapy is first discussed	☐
At subsequent visit	☐
Just prior to chemotherapy administration	☐
Other	☐

If "Other"

Are there some patients who receive chemotherapy *without* structured verbal information about neutropenic sepsis? Yes

Is there a documented template or checklist for use while giving verbal information about neutropenic sepsis which is in routine use (a list of discussion points for example)? Yes

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Section 2c – Criteria for seeking advice or assistance

In many centres, if patients who received chemotherapy become unwell, they are asked to seek advice. Is this the case for your centre? Yes

Working Hours:
Who are they advised to contact? Dedicated telephone service (same number all day)
If Other

Outside working hours:
Who are they advised to contact? Dedicated telephone service (same number all day)
If Other

Please describe the temperature criteria patients are advised to use. If your policy does not fit neatly in the boxes below, please describe it in the "other" box.

Single temperature ***above*** which patients are advised to seek advice immediately °C
Or °C over Hours

Single temperature ***below*** which patients are advised to seek advice immediately °C
(Please state "none" if not mentioned in advice)

Other temperature criteria

The following question mainly concerns paediatric patients
Does your advice regarding seeking a medical opinion cover changes which may be observed by a parent or carer (for example lethargy or behavioural change)? Yes

Other Symptoms patients are advised about

Do you have any patient experience / satisfaction survey results which cover the information patients receive concerning neutropenic sepsis? Yes

If so, please forward a copy.

Section 3 – Assessment and initial management in Secondary / Tertiary Care

On arrival in hospital, an assessment generally takes place to determine whether the patient is treated with a "neutropenic sepsis regimen". The criteria for putting a patient on this pathway have already been found to vary. Again, we are looking for what your hospital policy is.

Temperature criteria for in-hospital assessment can vary from those given in patient information, which is why we are asking for it again.

Section 3a – Initial Assessment

We are aware that when deciding whether to treat someone as possibly having neutropenic sepsis, some centres use different criteria to those in section 2.

What temperature would qualify a patient for treatment as neutropenic sepsis? If your policy does not fit neatly in the boxes below, please describe it in the "other temperature criteria" box.

Single temperature ***at or above*** which patients are treated for neutropenic sepsis °C

Or °C over Hours

Single temperature ***below*** which patients are treated for neutropenic sepsis °C

Other temperature criteria

Other symptoms or criteria

What neutrophil count do you use, below which you treat as neutropenic sepsis? If this does not adequately describe your policy, please use the "other information" box.

$x10^9/L$

Other Information:

Section 3b – IV Empirical Antibiotics

Do some patients with suspected neutropenic sepsis receive antibiotics routinely before the FBC result is available? Yes

If yes, how is this decided? All patients suspected of neutropenic sepsis

If you use a risk assessment tool or rules to decide whether a patient receives immediate empirical antibiotics before FBC result is known, please summarise it below or (if easier) attach a copy in your reply.

Do you have a target "door to needle" time for administration of the initial IV antibiotics?

Yes

If so, how long is this target? hours

Who does this apply to? All patients suspected of neutropenic sepsis

If the risk stratification is different to the above, please summarise your criteria below.

Where a patient receives empirical IV antibiotics, please select which antibiotic(s) are routinely given in your hospital in the following circumstances. It is likely that you do not have a policy to cover each situation, so please tick the "no protocol" box where applicable.

IV antibiotics routinely given?

No protocol in this situation ☐

- Amikacin ☐
- Ceftazadime ☐
- Ceftriaxone ☐
- Ciprofloxacin ☐
- Gentamicin ☐
- Imipenem ☐
- Linezolid ☐
- Meropenem ☐
- Piperacillin/Tazobactam (Tazocin) ☐
- Teicoplanin ☐
- Vancomycin ☐
- Other

IV antibiotics used if following a "Higher Risk" protocol?

No protocol in this situation ☐

- Amikacin ☐
- Ceftazadime ☐
- Ceftriaxone ☐
- Ciprofloxacin ☐
- Gentamicin ☐
- Imipenem ☐
- Linezolid ☐
- Meropenem ☐
- Piperacillin/Tazobactam (Tazocin) ☐
- Teicoplanin ☐
- Vancomycin ☐
- Other

Any changes if there is a central line in situ and infection *not* expected clinically?

No protocol in this situation ☐

- Amikacin ☐
- Ceftazadime ☐
- Ceftriaxone ☐
- Ciprofloxacin ☐
- Gentamicin ☐
- Imipenem ☐
- Linezolid ☐
- Meropenem ☐
- Piperacillin/Tazobactam (Tazocin) ☐
- Teicoplanin ☐
- Vancomycin ☐
- Other

Any changes where line sepsis suspected clincially?

No protocol in this Situation ☐

- Amikacin ☐
- Ceftazadime ☐
- Ceftriaxone ☐
- Ciprofloxacin ☐
- Gentamicin ☐
- Imipenem ☐
- Linezolid ☐
- Meropenem ☐
- Piperacillin/Tazobactam (Tazocin) ☐
- Teicoplanin ☐
- Vancomycin ☐
- Other

Any changes with penicillin allergy (thought to have a **low** risk of anaphylaxis to penicillin)?

No protocol in this situation ☐

- Amikacin ☐
- Ceftazadime ☐
- Ceftriaxone ☐
- Ciprofloxacin ☐
- Gentamicin ☐
- Imipenem ☐
- Linezolid ☐
- Meropenem ☐
- Piperacillin/Tazobactam (Tazocin) ☐
- Teicoplanin ☐
- Vancomycin ☐
- Other

Any changes with penicillin allergy (thought to have a **high** risk of anaphylaxis to penicillin)?

No protocol in this situation ☐

- Amikacin ☐
- Ceftazadime ☐
- Ceftriaxone ☐
- Ciprofloxacin ☐
- Gentamicin ☐
- Imipenem ☐
- Linezolid ☐
- Meropenem ☐
- Piperacillin/Tazobactam (Tazocin) ☐
- Teicoplanin ☐
- Vancomycin ☐
- Other

Other aspects of your antibiotic policy not adequately covered by the above

Section 3c – Empirical Oral Antibiotics

Are some patients with confirmed or suspected neutropenic sepsis started on oral antibiotics immediately (without receiving IV antibiotics? Yes

Please summarise your criteria for administration of early oral (instead of IV) antibiotics below

Please summarise the criteria for ***excluding*** the patient from early oral antibiotics

If used, please could you forward a copy of the risk assessment tool / assessment process used to decide whether oral antibiotic therapy is appropriate?

If a patient is immediately started on oral antibiotics, when are they routinely sent home?

Immediately

If observed, for how long? days

What oral antibiotics are routinely used?

- Amoxicillin ☐
- Ciprofloxacin ☐
- Co-amoxiclav ☐
- Clarythromycin ☐
- Levofloxacin ☐

Other

Are these patients sent home with specific written information? Yes
If so, please forward a copy of this information in your reply.

Do you have any outcome data regarding patients discharged "early" on oral antibiotics?

Yes

If so, please include a copy of the outcome data report in your reply.

Section 3d – Policy Documents

Does your hospital have a written neutropenic sepsis policy? Yes

Does your hospital have a written care pathway detailing the steps in the assessment and admission of patients with suspected neutropenic sepsis separate from your neutropenic sepsis policy document?

Yes

Does your hospital have a specific neutropenic sepsis antibiotic policy? Yes

Please include the relevant sections of these documents in your reply.

Section 4 – Ongoing management of patients with neutropenic sepsis
This section considers the in-patient management of patients with neutropenic sepsis

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Section 4a – Management of the uncomplicated patient

If a patient has been admitted with neutropenic sepsis, is on IV antibiotics, is progressing without complications and has become apyrexial, would they routinely be changed to oral antibiotics?

Yes

If so, when would this change routinely occur? After a set number of days
If a set time applies to the above, how long? days
If other, please explain criteria

Would they be observed for a period of time after stopping IV antibiotics before discharge?

Yes

If yes, how long?

Are your patients ever routinely discharged on **intravenous antibiotics** which will be administered as an out-patient or at home? Yes

If so, please summarise your criteria for starting outpatient intravenous antibiotics below

Please summarise the criteria for ***excluding*** the patient from being discharged on IV antibiotics

Section 4b – Management of the complicated neutropenic sepsis patient

It is assumed that if a causative organism responsible for the neutropenic sepsis is cultured, antibiotics are immediately changed to account for the sensitivities of the organism. If this is *not* the case, please explain your usual policy here.

The rest of this section assumes no positive culture and continuation of empirical treatment.

If a patient remains pyrexial, neutropenic and is not showing clinical or biochemical (inflammatory markers) improvement, after how long would you consider a change to second line empirical antibiotic treatment? 1 day

Section 5 – Prophylaxis of neutropenic sepsis

This section covers antibiotic and growth factor prophylaxis of bacterial infections causing neutropenic sepsis, both primary and secondary. Please note that the scope of this survey does not cover PCP, viral or fungal prophylaxis, but if, for example, co-trimoxazole is given as prophylaxis against *bacterial* infection, we would like to know about it.

If chemotherapy is not given in your hospital (or you are not an oncologist and do not have easy access to this information) then please move on to section 6

If you have a written neutropenic sepsis prophylaxis protocol or policy, please forward a copy to us in your reply.

Section 5a – Primary Prophylaxis (Antibiotics)

Do you routinely give primary prophylaxis with antibiotics for some or all chemotherapy regimens?

Yes - all regimens

If "Other Criteria"

Please give any further information regarding the selection of patients receiving primary prophylaxis with antibiotics.

Please state which antibiotics you use for primary prophylaxis against **bacterial** infection (excluding PCP and anti-fungal prophylaxis).

Section 5b – Primary Prophylaxis (Growth Factors such as GCSF)

Do you routinely give primary prophylaxis with growth factors for some or all chemotherapy regimens? Yes - all regimens

If "Other Criteria"

Please give any further information regarding the selection of patients receiving primary prophylaxis with growth factors.

What type of growth factors do you use for primary prophylaxis? GCSF (administered daily)
If further clarification required, please enter here

Section 5c – Secondary Prophylaxis (Antibiotics)

After an episode of neutropenic sepsis, do you routinely give secondary prophylaxis with antibiotics for some or all chemotherapy regimens? Yes - all regimens

Please give any further information regarding the selection of patients receiving secondary prophylaxis with antibiotics.

Please state which antibiotics you use for secondary prophylaxis against **bacterial** infection (excluding PCP and anti-fungal prophylaxis)

Section 5d – Secondary Prophylaxis (Growth Factors such as GCSF)

After an admission with neutropenic sepsis, do you routinely give secondary prophylaxis with growth factors for some or all chemotherapy regimens? Yes - all regimens

Please give any further information regarding the selection of patients receiving secondary prophylaxis with growth factors.

Which growth factors do you use for secondary prophylaxis? GCSF (administered daily)
If further clarification required, please enter here

Section 6 – Patient Experience of Admission for Neutropenic Sepsis

Do you have written information for patients admitted with neutropenic sepsis? Yes

If so, please include a copy of this with your reply.

Please also forward any patient satisfaction survey results or focus group / patient forum minutes regarding admissions for neutropenic sepsis.

Section 7 – Training for Healthcare Professionals

Is treatment of neutropenic sepsis covered in your induction program, for new junior doctors who are likely to encounter it? Yes

Does your ongoing junior doctor education program cover neutropenic sepsis? Yes

Do you have a handbook containing information on the management of neutropenic sepsis for your junior doctors and/or nurses? Yes

Is there specific educational material or ongoing training for nursing staff regarding neutropenic sepsis? Yes

Is your neutropenic sepsis policy available on your intranet? Yes

Do you think this is easy for your junior staff to locate? Yes

Are there posters or other readily accessible information concerning the management of neutropenic sepsis available in the admitting ward (for example A&E /MAU) Yes

Please send copies of this teaching or instructional material with your reply.

Section 8 – Further information

Many thanks for completing this survey, and we appreciate the effort you have gone to.

To assess the burden of neutropenic sepsis to the NHS, we intend to organise a further follow-up survey in a small number of representative institutions chosen at random. In order to easily participate, it is important that your hospital uses electronic medical records and / or electronic discharge summaries. If you would be willing for us to approach **one of your trainees** to help us with this if we need to, please let us know below.

We have electronic notes or discharge summaries

You may approach one of our trainees

List of documents requested – please indicate those which are attached

Written information given to patients pre-chemotherapy about neutropenic sepsis	See Attached
Neutropenic Sepsis Alert Card	See Attached
Patient Experience Survey (Neutropenic Sepsis Information)	See Attached

Risk assessment tool for giving IV antibiotics before FBC available	See Attached
Neutropenic Sepsis antibiotic policy	See Attached
Risk assessment tool for deciding whether to give early oral antibiotics	See Attached
Patient information for when patients discharged on oral antibiotics without having received IV antibiotics	See Attached
Neutropenic Sepsis Policy	See Attached
Neutropenic Sepsis Patient Pathway	See Attached
Neutropenic Sepsis clerking document	See Attached
Neutropenic sepsis prophylaxis (primary and secondary, growth factors and antibiotics)	See Attached
Information for patients following admission for neutropenic sepsis	See Attached
Patient satisfaction survey (or focus group / patient forum minutes) regarding neutropenic sepsis admission	See Attached
Poster (or similar) regarding neutropenic sepsis	See Attached
Educational material available to junior doctors	See Attached

Acknowledgements

The efforts of all those who took the time to complete the neutropenic sepsis questionnaire are very much appreciated. It is recognised that completing the questionnaire and gathering the supporting documentation took a considerable amount of time and effort.

My thanks to Vanessa Feam and her team at the Office of National Statistics for their assistance with this work.

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